REMARKS

Applicants respectfully request entry of the amendment and reconsideration of the claims. Claim 3 has been amended to incorporate the subject matter of claim 15. Claim 16 has been amended to depend from claim 3. Claims 15, 50-56 and 74-80 have been cancelled without prejudice or disclaimer. After entry of the amendment, claims 3-14 and 16-24 will be pending.

Rejections under 35 USC § 102

(1) Claims 3-6, 8-14, 22-24, and 74-79 were rejected under 35 U.S.C. 102(b) as being allegedly anticipated by Gravel et al. (US 6,458,764; hereinafter "Gravel").

Without acquiescing to the rejection and solely for the purpose of advancing prosecution, claims 74-79 have been cancelled without prejudice or disclaimer. Applicants reserve the right to pursue the cancelled subject matter in one or more continuation and/or divisional applications.

Regarding the rejection of claims 3-6, 8-14 and 22-24, claim 3 has been amended to incorporate the subject matter of claim 15, which is not subject to the present rejection under 35 USC § 102(b). Applicants respectfully submit that Gravel does not disclose a method of increasing muscle function in a subject suffering from wasting that comprises administering to the subject a GRF analog of formula A (see claim 3), as recited in claim 3. As such, Applicants respectfully submit that Gravel does not disclose all the elements of claim 3 as amended. Claims 4-6 and 8-14 depend directly or indirectly from claim 3 and are therefore not anticipated by Gravel for the same reason.

In view of the foregoing, Applicants submit Gravel does not disclose all the elements of the claims. Withdrawal of the rejection is respectfully requested.

(2) Claims 3-14, 22-24, and 74-80 were rejected under 35 U.S.C. 102(b) as being allegedly anticipated by Larocque et al. (APS poster, 2001; hereinafter "Larocque").

Without acquiescing to the rejection and solely for the purpose of advancing prosecution, claims 74-80 have been cancelled. Applicants reserve the right to pursue the cancelled subject matter in one or more continuation and/or divisional applications.

Regarding the rejection of claims 3-14 and 22-24, claim 3 has been amended to incorporate

the subject matter of claim 15 which was not subject to the present rejection under 35 U.S.C. 102(b). Applicants respectfully submit that Larocque does not disclose a method of increasing muscle function in a subject suffering from wasting that comprises administering to the subject a GRF analog of formula A, as recited in claim 3. As such, Applicants respectfully submit that Larocque does not disclose all the elements of claim 3 as amended. Claims 4-6 and 8-14 depend directly or indirectly from claim 3 and are therefore not anticipated by Larocque for the same reason.

In view of the foregoing, Applicants submit Larocque does not disclose all the elements of the claims. Withdrawal of the rejection is respectfully requested.

Rejections under 35 USC § 103

(1) Claims 50-55 were rejected under 35 U.S.C. 103(a) as being allegedly unpatentable over Gravel et al. (US 6,458,764; hereinafter "Gravel"). Without acquiescing to the rejection and solely for the purpose of advancing prosecution, claims 50-55 have been cancelled without prejudice or disclaimer. The rejection is therefore moot. Applicants reserve the right to pursue the cancelled subject matter in one or more continuation and/or divisional applications.

(2) Claims 50-56 were rejected under 35 U.S.C. 103(a) as being allegedly unpatentable over Larocque et al. (APS poster, 2001; hereinafter "Larocque"). Without acquiescing to the rejection and solely for the purpose of advancing prosecution, claims 50-55 have been cancelled without prejudice or disclaimer. The rejection is therefore moot. Applicants reserve the right to pursue the cancelled subject matter in one or more continuation and/or divisional applications.

(3) Claims 15-21 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Schwartz et al. (U.S. 6,423,693; hereinafter "Schwartz") in view of Gravel et al. (US 6,458,764; hereinafter "Gravel") or Larocque et al. (APS poster, 2001; hereinafter "Larocque"). Applicants respectfully traverse this rejection.

For the purposes of the discussion below, growth hormone is referred to as "GH". Further, growth hormone-releasing factor (GRF) and growth hormone releasing hormone (GHRH) are two different terms which refer to the same molecule and therefore are interchangeable.

To make a *prima facie* case of obviousness, all the limitations of the claims must be taught or suggested in the references cited by the Office Action and all the teachings of the prior art need to suggest the claimed subject matter to the person of ordinary skill in the art. *In re Kotzab*, 217 F.3d 1365, 1370 (Fed. Cir. 2000). As articulated by the Supreme Court, a combination is obvious if it is no more than the predictable use of known elements according to their established functions; and there is a reason to combine the known elements. *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398 (2007). "[I]t remains necessary to identify the reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed." *Id.* Applicants submit that the Office Action has failed to make the required *prima facie* case, as the cited references, either alone or in combination, do not teach or suggest all the claim limitations and lack sufficient reason to combine.

The subject matter of claim 15 (now canceled) has been incorporated into claim 3, which relates to a method of increasing muscle function in a subject suffering from wasting comprising administering to the subject a GRF analog of formula A.

Schwartz discloses that GHRH stimulates GH production and secretion, and that there is a need for an effective medicinal approach which directly promotes preservation of muscle mass. Schwartz discloses that insulin growth factor-1 (IGF-1) is the major growth factor promoting the differentiation of muscle cells and increasing muscle mass, and that hGH (human GH) has been shown to preserve lean body mass in animal studies and is in use in many clinical trials for this indication. Based on these effects of IGF-1 and hGH on muscle mass, Schwartz proposes that the *in vivo* expression of GHRH from a vector, by virtue of its stimulation of GH and IGF-1, may be used for the treatment of cachexia.

Gravel discloses GRF (growth hormone-releasing factor) analogs of formula A recited in the Office Action, and that these analogs possess enhanced biological activity relative to native GRF and are capable of increasing blood levels of GH and IGF-1 upon administration.

Larocque discloses that the GRF analogue (hexenoyl trans-3)hGRF(1-44)NH_2 (referred to as TH9507), containing a covalently bound hydrophobic moiety, shows increased stability and GH-releasing potency relative to native GRF.

None of Schwartz, Gravel, or Larocque, alone or in combination, disclose or suggest that a GRF analog of formula A may be useful for increasing muscle function in a subject suffering from

wasting. As noted above, Schwartz is only concerned with increasing muscle mass, and presumes, solely based on the known effects of IGF-1 and GH on muscle mass, that the *in vivo* expression of GHRH from a vector, by stimulating GH and IGF-1, may be used for the treatment of cachexia.

However, Schwartz does not demonstrate the effect of *in vivo* administration of GHRH from a vector on muscle mass, and does not even disclose or suggest that muscle function may be increased. Applicants respectfully submit that an increase in muscle mass is not in itself indicative or predictive of an increase in muscle function. Several clinical studies have shown that rhGH (recombinant hGH) administration has an effect on muscle mass, but not on muscle function, such as muscle strength.

For example, Zachwieja and Yarasheski (*Physical Therapy* **79**(1): 76-82, enclosed as Appendix A) summarize the findings of various studies in which the effects of recombinant GH administration on muscle force in older men and women were investigated (see more particularly the table at page 78). No significant effects were observed in three of the four studies in which muscle force was assessed, and a slight effect (increase of 14% over placebo) was reported in one study performed on 5 patients only. However, the results obtained in this contradictory study appear difficult to explain, as noted by Zachwieja and Yarasheski at page 79, left column, first full paragraph. From these studies, the authors concluded the following at page 79, left column, second full paragraph:

> *"Almost unequivocally, rhGH administration has been reported to increase lean body mass in men and women aged 60 years or older. Maximum muscle force production (MVC, 1-RM) and functional ability, however, have not been improved in parallel with the increments in lean mass. It appears doubtful, therefore, that the increments in lean body mass are occurring in the skeletal muscle, specifically the skeletal muscle contractile proteins."* (emphasis added)

In another article summarizing the findings of various studies in which the effects of recombinant GH administration on muscle mass and/or function (enclosed as Appendix B), Lissett and Shalet conclude that GH therapy has resulted in an increase in lean body mass, but functional ability and strength have not improved in the majority of studies, and that clear-cut beneficial effects of GH on muscle and bone in GH-replete individuals have not been demonstrated (see Summary).

Similarly, Burdet *et al.* (enclosed as Appendix C) discloses that the daily administration of 0.15 IU/kg of rhGH during 3 weeks increases lean body mass but does not improve muscle strength or exercise tolerance in underweight patient with COPD (see the last sentence of the abstract). In an uncontrolled (*i.e.*, no placebo) and unblinded study on seven COPD patients published in 1991 (enclosed as Appendix D), Pape *et al.* reported an improvement in maximal inspiratory pressure after GH treatment. However, as noted in Pape *et al.* on page 1498, right column, penultimate paragraph, the results were preliminary and required follow-up with placebo-controlled, blinded studies. In fact and as noted above, the beneficial effect of GH administration on muscle strength/function has not been observed in several subsequent clinical studies.

In contrast, the present inventors have surprisingly shown in a randomized, double-blind, placebo-controlled study, that administration of a representative GRF analog of formula A, (hexenoyl trans-3)hGRF(1-44)NH_2, to subjects with stable COPD, increases muscle function (Example 6).

Therefore, as evidenced for example by the references in attached Appendices A-D, the skilled person would not presume that an increase in muscle mass may be directly and unequivocally extrapolated to an increase in muscle function. The references in Appendices A-D suggest the exact opposite, as the overall observation in the studies is that while GH therapy is regularly correlated with an increase in muscle mass, the same does not hold true for muscle function.

In view of the foregoing, Applicants respectfully submit the combination of references does not disclose or suggest all the elements of claim 3 and provides no motivation or reasonable expectation of success for one of skill in the art to increase muscle function in a subject suffering from wasting via administration of a GRF analog of formula A, as recited in claim 3. Applicants therefore submit that claims 3 and 16-21 are non-obvious over Schwartz in combination with Gravel or Larocque. Withdrawal of the rejection is respectfully requested.

(4) Claims 50-56 were rejected under 35 U.S.C. § 103(a) a being unpatentable over U.S. 7,316,997 or U.S. 20090011985 or U.S. 20090253623 or U.S. 20090088383. Without acquiescing to the rejection and solely for the purpose of advancing prosecution, claims 50-55 have been cancelled without prejudice or disclaimer. The rejection is therefore moot. Applicants reserve the right to

pursue the cancelled subject matter in one or more continuation and/or divisional applications.

(5) Claims 15-21 were rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. 7,316,997 or U.S. 20090011985 or U.S. 20090253623 or U.S. 20090088383 in view of Schwartz et al. (U.S. 6,423,693; hereinafter "Schwartz").

Regarding U.S. 7,316,997 (Abribat *et al.*), it is believed that this reference was intended, rather than U.S. 7,316,977 (Siddiqui *et al.*) mentioned in the Office Action, based on the similarity in serial numbers and the Office Action's comments regarding a common inventor and common ownership.

Enclosed with the present response is a Statement of Common Ownership pursuant to 35 U.S.C. § 103(c), by France Leclaire (Assistant Director, Intellectual Property Management, at Theratechnologies Inc., the instant assignee) stating that the present application and U.S. 7,316,997, U.S. 20090011985, U.S. 20090253623 and U.S. 20090088383, were, at the time the invention of the present application was made, commonly owned by or subject to an obligation of assignment to Theratechnologies Inc. Therefore, in view of the foregoing and pursuant to 35 U.S.C. 103(c), Applicants respectfully submit that U.S. 7,316,997, U.S. 20090011985, U.S. 20090253623 and U.S. 20090088383 do not qualify as prior art under 35 U.S.C. 103, and consequently cannot be asserted in a rejection under 35 U.S.C. 103(a) against the present application.

Withdrawal of the rejection is respectfully requested.

Double Patenting Rejections

(1) Claims 3-14, 22-24, 50-56 and 74-80 were rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-8 of U.S. 7,316,997.

Applicants respectfully traverse the rejection. First and as noted above, claims 50-56 and 74-80 have been cancelled, thereby rendering moot any rejection thereof.

Second, claim 3 has been amended to incorporate the subject matter of claim 15, which was not rejected on the grounds of nonstatutory obviousness-type double patenting in view of claims 1-8 of U.S. 7,316,997. As such, claim 3 as amended corresponds to claim 15, and new claims 4-14 and 22-24 depend directly or indirectly from claim 3.

Finally, claims 1-8 of U.S. 7,316,997 relate to the treatment of HIV-related lipodystrophy, whereas instant claims 3-14 and 16-21 relate to a different treatment, namely increasing muscle function in a subject suffering from wasting.

In view of the foregoing, Applicants submit the claims as amended are non-obvious over claims 1-8 of U.S. 7,316,997. Reconsideration and withdrawal of the rejection is respectfully requested.

(2) Claims 15-21 on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-8 of U.S. 7,316,997, in further view of Schwartz et al. Applicants respectfully traverse this rejection.

As noted above, claim 3 has been amended and corresponds to claim 15 (now cancelled). Claims 1-8 of U.S. 7,316,997 relate to the treatment of HIV-related lipodystrophy, whereas instant claims 3 and 16-21 relate to a different treatment, namely increasing muscle function in a subject suffering from wasting.

As discussed above, Schwartz is only concerned with increasing muscle mass, and presumes, solely based on the known effects of IGF-1 and GH on muscle mass, that the *in vivo* expression of GHRH from a vector, by stimulating GH and IGF-1, may be used for the treatment of cachexia. However, Schwartz does not demonstrate the effect of *in vivo* administration of GHRH from a vector on muscle mass, and does not even disclose or suggest that muscle function may be increased.

Furthermore, several clinical studies, as evidenced by the references in attached Appendices A-D, have shown that rhGH administration has an effect on muscle mass, but not on muscle function, such as muscle strength. Thus, Applicants respectfully submit the cited combination of references does not provide any motivation or reasonable expectation of success for one of skill in the art to use GRF analogs of formula A to stimulate GH secretion and increase muscle function in a subject suffering from wasting, as claimed in instant claims 3 and 16-21.

Applicants therefore respectfully submit that claims 3 and 16-21 as amended are non-obvious over claims 1-8 of U.S. 7,316,997 in combination with Schwartz. Withdrawal of the rejection is respectfully requested.

(3) Claims 3-14, 22-24, 50-56 and 74-80 were provisionally rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-88 of copending Application No. 12/239,697; claims 1-88 of copending Application No. 12/239,708; or claims 1-88 of copending Application No. 12/239,712. Applicants respectfully traverse the rejection.

First and as noted above, claims 50-56 and 74-80 have been cancelled, thereby rendering moot any rejection thereof.

Regarding the rejection of claims 3-14 and 22-24, claim 3 has been amended to incorporate therein the subject matter of claim 15, which was not rejected on the grounds of nonstatutory obviousness-type double patenting in view of the claims of copending Applications Nos. 12/239,697, 12/239,708 or 12/239,712. As such, claim 3 as amended corresponds to former claim 15, and new claims 4-14 and 22-24 depend directly or indirectly from claim 3.

Furthermore, the claims of copending Application No. 12/239,697 relate to the improvement of daytime vigilance and/or cognitive function in a subject, the claims of copending Application No. 12/239,708 relate to the alteration of a lipid parameter in a subject, the claims of copending Application No. 12/239,712 relate to the alteration of a first body composition parameter in a subject, and thus differ from instant claims 3-14 and 16-21, which relate to increasing muscle function in a subject suffering from wasting.

In view of the foregoing, Applicants submit that claims 3-14 and 22-24 as amended are non-obvious over the cited copending applications. Reconsideration and withdrawal of the rejection is respectfully requested.

(4) Claims 15-21were provisionally rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 20-34 and 89-104 of copending Application No. 11/877,395; claims 1-88 of copending Application No. 12/239,697; claims 1-88 of copending Application No. 12/239,708; or claims 1-88 of copending Application No. 12/239,712 in further view of Schwartz et al. Applicants respectfully traverse the rejection.

Applicants respectfully submit that:

- Claims 20-34 and 89-104 of copending Application No. 11/877,395 relate to the

treatment of HIV-related lipodystrophy without impairing glucose control in a subject;

- The claims of copending Application No. 12/239,697 relate to the improvement of daytime vigilance and/or cognitive function in a subject;
- The claims of copending Application No. 12/239,708 relate to the alteration of a lipid parameter in a subject; and
- The claims of copending Application No. 12/239,712 relate to the alteration of a first body composition parameter in a subject;

Thus, the claims of the cited copending applications differ from the subject matter of instant claims 3 and 16-21, which relate to increasing muscle function in a subject suffering from wasting.

As discussed above, Schwartz is only concerned with increasing muscle mass, and presumes, solely based on the known effects of IGF-1 and GH on muscle mass, that the *in vivo* expression of GHRH from a vector, by stimulating GH and IGF-1, may be used for the treatment of cachexia. However, Schwartz does not demonstrate the effect of *in vivo* administration of GHRH from a vector on muscle mass, and does not even disclose or suggest that muscle function may be increased.

Furthermore, several clinical studies, as evidenced by the references in attached Appendices A-D, have shown that rhGH administration has an effect on muscle mass, but not on muscle function, such as muscle strength. Thus, as discussed above, Applicants submit the combination of references does not provide any motivation or reasonable expectation of success for one of skill in the art to use GRF analogs of formula A to stimulate GH secretion, and in turn to increase muscle function in a subject suffering from wasting, as claimed in instant claims 3 and 16-21.

Applicants respectfully submit that claims 3 and 16-21 as amended are non-obvious over claims 20-34 and 89-104 of copending Application No. 11/877,395, the claims of copending Applications Nos. 12/239,697, 12/239,708 or 12/239,712, in further view of Schwartz. Withdrawal of the rejection is respectfully requested.

Conclusion

Favorable consideration is respectfully requested. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Respectfully submitted,

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